08-08-05

1626

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Our Ref.:446.037

In re Application of:	:	
Corbier, et al	:	
Serial No.: 10/009,407	:	Group: 1626
Filed: 1/25/2002	:	
For: NEW...ANTI-FUNGALS	:	Examiner: Rei Tsang Shiao

Hedmen & Costigan
1185 Avenue of the Americas
New York, NY 10036

August 5, 2005

SUPPLEMENTAL RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria 22313-1450

Sir:

Supplemental to the amendment of July 7, 2005, applicants are submitting herewith a certified copy of the French priority application and a sworn English translation thereof so the present application is entitled to the benefit of the French filing date of June 9, 1999 which removes the Courtin WO 99/29716 as a reference.

In view of the remarks presented in the amendment of June 20, 2005, it is believed that the application is in condition for allowance. Therefore, favorable reconsideration of the application is requested.

Respectfully submitted,
Hedman & Costigan

Charles A. Muserlian #19,683
Attorney for Applicants
Tel#(212)302-8989

CAM:dn

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Date of Deposit: August 5, 2005

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D. Nakonieczny

Diane Nakonieczny

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF TRANSLATION

Honourable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

I, JOHN CHARLES McGILLEY, B.A. M.I.T.I., Technical Translator, of c/o Priory Translations Limited, 11, Magdalen Street, Colchester, Essex, England,

hereby state:

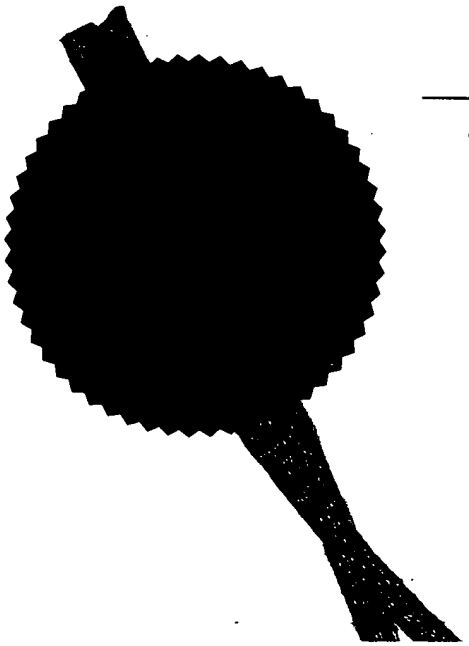
THAT I am well acquainted with the French and English languages.

THAT I translated the document identified as the Certificate of the French National Institute of Industrial Property and of the certified true copy of the French Patent Application No. 99 07252 filed at the National Institute of Industrial Property on 9th June 1999, from French into English;

THAT the attached English translation is a true and correct translation of French Patent Application No. 99 07252

to the best of my knowledge and belief; and

THAT all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true and further, that these statements are made with the knowledge that wilful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code



JOHN CHARLES McGILLEY

A

FRENCH REPUBLIC

NATIONAL INSTITUTE OF INDUSTRIAL PROPERTY

PATENT OF INVENTION

UTILITY CERTIFICATE - CERTIFICATE OF ADDITION

OFFICIAL COPY

The Director General of the National Institute of Industrial Property certifies that the document annexed hereto is the certified true copy of an application for title of industrial property registered at the Institute.

Drawn up in Paris 18th July 2005

For the Director General of the
National Institute of Industrial
Property

The Head of the Patent Department

[signed]
Martine PLANCHE

B

INVENTION PATENT, UTILITY CERTIFICATE

NATIONAL INSTITUTE OF
INDUSTRIAL PROPERTY

REQUEST FOR GRANT

Confirmation of filing by fax ☐

Date of delivery of documents 9 JUNE 1999 National Registration number 9907252 Postal code of place of filing 75 INPI PARIS Date of filing 9 JUNE 1999	**1 NAME AND ADDRESS OF APPLICANT OR REPRESENTATIVE TO WHOM ALL CORRESPONDENCE SHOULD BE ADDRESSED** Hoechst Marion Roussel Madame TONNELLIER Marie-José 102 route de Noisy 93235 ROMAINVILLE CEDEX No. of permanent Power of Attorney: — Ref of correspondent: ML/2519 Telephone: 0149915410

2. APPLICATION nature of industrial property right

☒ invention patent ☐ divisional application

☐ utility certificate ☐ conversion of a European Patent Application ⇒ **initial application** ⇓ ☐ invention patent ☐ utility certificate No. date

Establishment of search report ☐ deferred ☒ immediate

The Applicant requires payment by instalments of the fees ☐ yes ☒ no

Title of the invention (200 characters maximum)

New derivatives of echinocandin, their preparation process and their use as antifungal agents.

3. APPLICANT (s) SIREN No. 552081473 APE-NAF code Name and forenames (underline patronymic name) or name Hoechst Marion Roussel Nationality FRENCH Complete Address 1, Terrasse Bellini 92800 PUTEAUX	Legal form Société Anonyme with a board of management and supervisory board Country FRANCE

If there is not enough space, continue on a blank sheet ☐

4. INVENTOR(S) The inventors are the applicants ☐ yes ☒ no If no, provide a separate designation

5. REDUCTION IN LEVEL OF FEES ☐ requested for the 1st time ☐ requested prior to filing; attach a copy of the admission decision

6. DECLARATION OF PRIORITY OR REQUEST FOR BENEFIT FROM THE FILING DATE OF A PREVIOUS APPLICATION

7. DIVISIONS previous to the present application

8. SIGNATURE OF APPLICANT OR REPRESENTATIVE (name and official capacity) **Marie-José TONNELLIER [signed]**	SIGNATURE OF RECEPTION OFFICER	SIGNATURE AFTER REG. OF APPLICATION AT I.N.P.I [signed]

C

INPI
National Institute of
Industrial Property
Patent Department

26 bis, rue de Saint Petersbourg
7500 Paris Cedex 08
Tel: 01 53 04 53 04 Fax: 01 42 94 86 54

PATENT OF INVENTION
Utility certificate
Intellectual property code – Book VI
Designation of inventor(s) Page no. 1 / 2

(If the applicant is not the inventor or the sole inventor)
This form must be completed clearly in black ink

Your references for this file (optional)		ML/2519	
National registration no.		9907252	
Title of the invention (200 characters or spaces maximum) New derivatives of echinocandin, their preparation process and their use as antifungal agents.			
Applicant(s): Marie-José TONNELLIER			
DESIGNATE(S) AS INVENTOR(S): (Indicate top right "Page no. 1/1". If there are more than three inventors, use an identical form and number each page, indicating the total number of pages).			
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Member company *(optional)*			
Name		FAUVEAU	
First names		Patrick	
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	Post code and town	93190	LIVRY-GARGAN
Member company *(optional)*			
Name		PIETRE-DISCHAMP	
First names		Nathalie	
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	Post code and town	94490	ORMESON SUR MARNE
Member company *(optional)*			
DATE AND SIGNATURE(S) OF APPLICANT(S) OR REPRESENTATIVE **(Name and capacity of signatory)** Marie-José TONNELLIER REPRESENTATIVE (signed)			

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D

INPI

National Institute of

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Patent Department

26 bis, rue de Saint Petersbourg

7500 Paris Cedex 08

Tel: 01 53 04 53 04 Fax: 01 42 94 86 54

PATENT OF INVENTION

Utility certificate

Intellectual property code – Book VI

Designation of inventor(s) Page no. 2 / 2

(If the applicant is not the inventor or the sole inventor)

This form must be completed clearly in black ink

Your references for this file (optional)		ML/2519	
National registration no.		9907252	
Title of the invention (200 characters or spaces maximum) New derivatives of echinocandin, their preparation process and their use as antifungal agents.			
Applicant(s): Marie-José TONNELLIER			
DESIGNATE(S) AS INVENTOR(S): (Indicate top right "Page no. 1/1". If there are more than three inventors, use an identical form and number each page, indicating the total number of pages).			
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Member company *(optional)*			
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	Post code and town	75017	PARIS
Member company *(optional)*			
Name			
First names			
Address	Street		
	Post code and town		
Member company *(optional)*			
DATE AND SIGNATURE(S) OF APPLICANT(S) OR REPRESENTATIVE **(Name and capacity of signatory)** Marie-José TONNELLIER REPRESENTATIVE (signed)			

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E

DOCUMENT INCLUDING AMENDMENTS

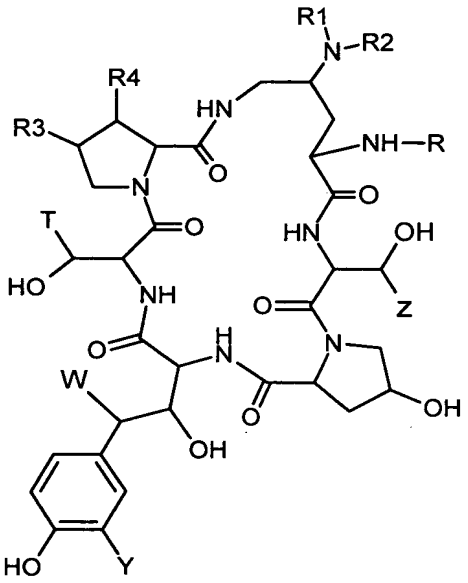
PAGE(S) OF THE DESCRIPTION OR OF THE CLAIMS OR SHEET(S) OF DRAWINGS			Amended claim	DATE OF THE CORRESPONDENCE	DATE STAMP OF CORRECTOR
Amended	Suppressed	Added			
27			X	5th May 2000	AMH 09 DEC. 2003

A change introduced in the drawing up of the original claims, except if the former results from the provisions of the Intellectual Property Code, is indicated by the mention "Amended Claims".

New derivatives of echinocandin, their preparation process and their use as antifungal agents.

The present invention relates to new derivatives of echinocandin, their preparation process and their use as antifungal agents.

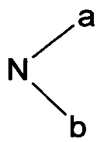
A subject of the invention is, in all possible isomeric forms as well as their mixtures, the compounds of formula (I):



(I)

in which

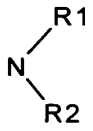
either R_1 and R_2, identical to or different from one other, represent a hydrogen atom, a hydroxyl radical, a linear, branched or cyclic alkyl radical containing up to 8 carbon atoms, optionally interrupted by an oxygen atom optionally substituted by an halogen atom, an OH radical, an



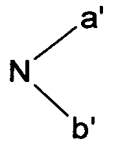
radical, a and b being identical to or different from one other, representing a hydrogen atom or an alkyl radical containing up to 8 carbon atoms, a and b can optionally form

with the nitrogen atom a heterocycle optionally containing one or more additional heteroatoms,

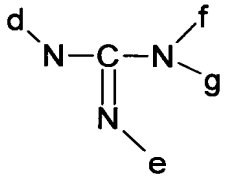
- or R_1 forms with the endocyclic carbon atom

carrying the  radical a double bond and/or R2

represents an XRa radical, X representing an oxygen atom or an NH or N-alkyl radical containing up to 8 carbon atoms and Ra represents a hydrogen atom, a linear, branched or cyclic alkyl radical containing up to 8 carbon atoms optionally substituted by one or more halogen atoms, by one or more OH, CO2H, CO2alk radicals,

by an 

radical, a' and b' representing a hydrogen atom, an alkyl radical containing up to 8 carbon atoms, a' and b' can form a heterocycle optionally containing one or more additional heteroatoms and/or by a heterocycle containing one or more heteroatoms or R2 represents a

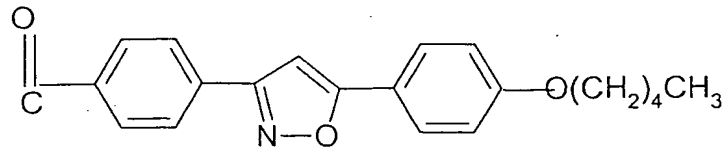


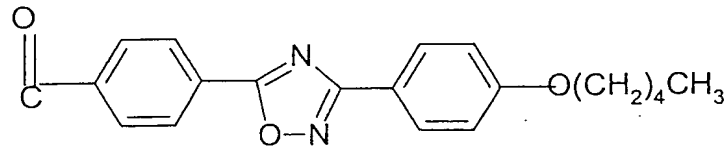
radical, in which d, e, f and g represent a hydrogen atom or an alkyl radical containing up to 8 carbon atoms, f and g can moreover represent an acyl radical containing up to 8 carbon atoms, e and f can also form a ring optionally containing one or more heteroatoms,

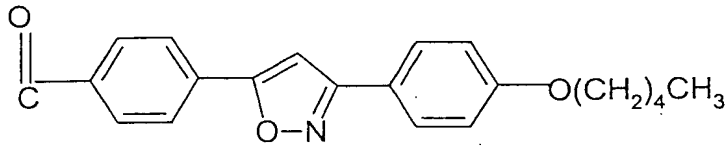
R_3 represents a hydrogen atom, a methyl or hydroxyl radical

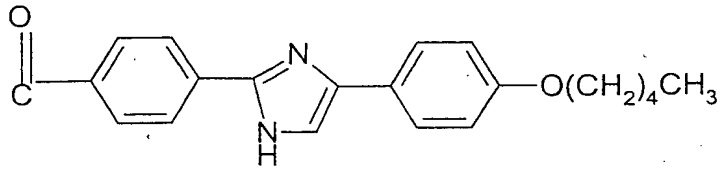
R_4 represents a hydrogen atom or a hydroxyl radical

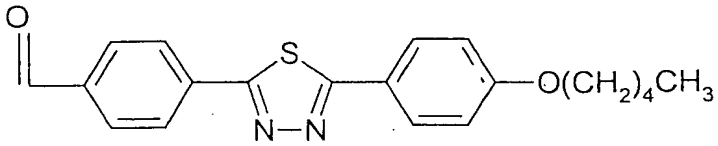
R represents a radical chosen from the following radicals:

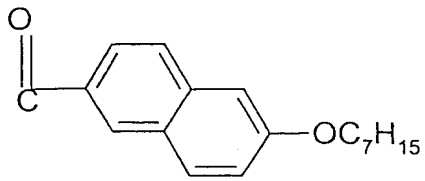

O
C
N
O
O(CH2)4CH3

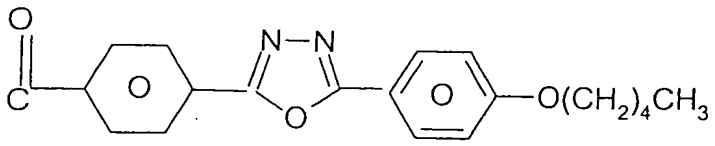

O
C
N
O
N
O(CH2)4CH3

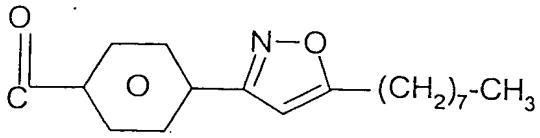

O
C
O
N
O(CH2)4CH3


O
C
N
N
H
O(CH2)4CH3


O
S
N
N
O(CH2)4CH3


O
C
OC7H15





T represents a hydrogen atom, a methyl radical, a CH2CONH$_2$, CH2C=N radical, a (CH2)2NH2 or (CH2)2Nalc+X- radical, X being a halogen atom and alk an alkyl radical containing up to 8 carbon atoms,

Y represents a hydrogen atom, a hydroxyl radical or halogen atom or an OSO3H radical or one of the salts of this radical,

W represents a hydrogen atom or an OH radical,

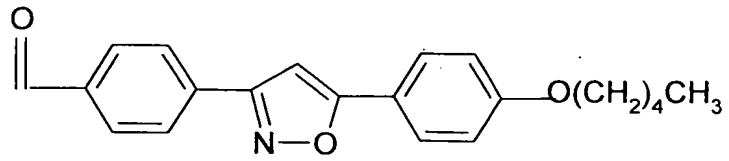
Z represents a hydrogen atom or a methyl radical,

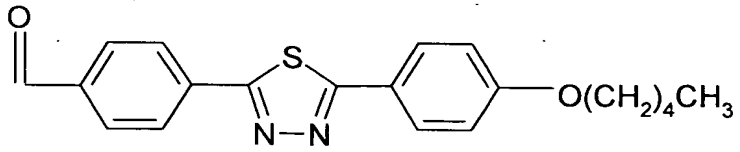
as well as the addition salts with acids of the products of formula (I).

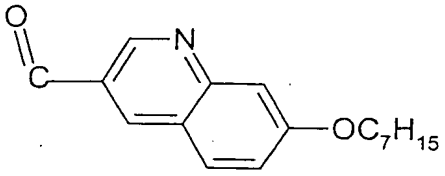
Among the addition salts with acids, those formed with mineral acids can be mentioned, such as hydrochloric, hydrobromic, sulphuric or phosphoric acids, or with organic acids such as formic, acetic, trifluoroacetic, propionic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic, alkanesulphonic acid, such as methane or ethane sulphonic, arylsulphonic acids such as benzene or paratoluenesulphonic acids.

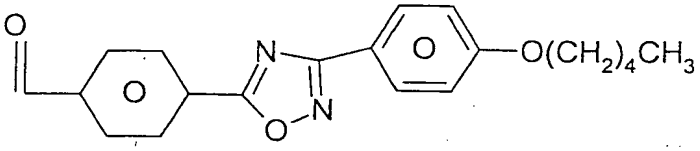
A more particular subject of the invention is the compounds of formula I in which T represents a hydrogen atom, those in which W represents a hydrogen atom, those in which Z represents a methyl radical, those in which Y represents a hydrogen atom, those in which R3 represents a methyl radical,

those in which R4 represents a hydroxyl radical and those in which R represents a

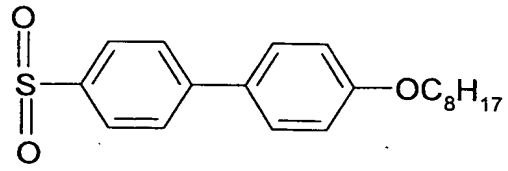








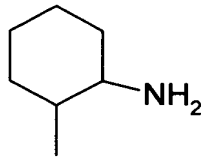
radical or a



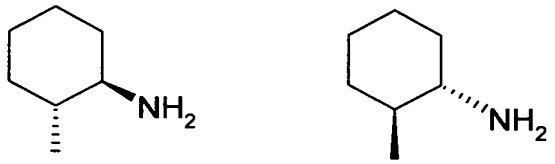
radical, those in which R1 represents a hydrogen atom, those in which R_2 represents a

(CH2)2 NH2

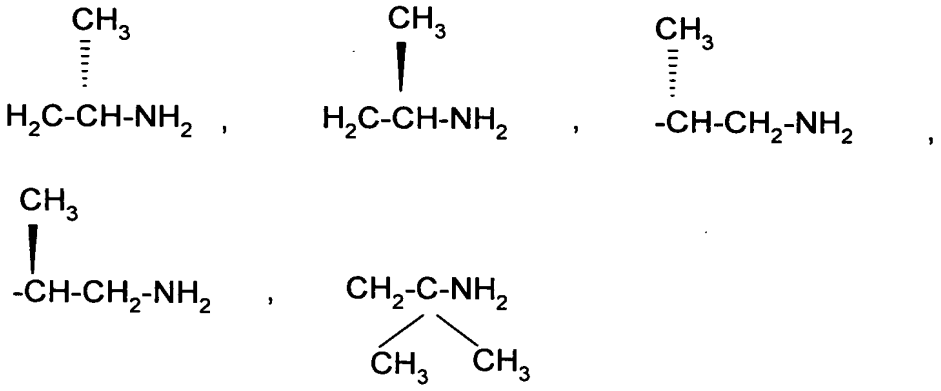
radical, those in which R2 represents a



radical and in particular the



radicals as well as those in which R2 represents a



radical.

A more particular subject of the invention is the compounds of formula I the preparation of which is given hereafter in the experimental part.

The compounds of formula (I) have useful antifungal properties; they are in particular active against Candida albicans and other Candida such as Candida glabrata, krusei, tropicalis, pseudotropicalis, parapsilosis and Aspergillus fumigatus, Aspergillus flavus, Cryptococcus neoformans.

The compounds of formula (I) can be used as medicaments

in humans or animals, in order to combat in particular digestive, urinary, vaginal or cutaneous candidoses, cryptococcoses, for example neuromeningeal, pulmonary or cutaneous cryptococcoses, bronchopulmonary and pulmonary aspergilloses and invasive aspergilloses in immunosuppressed patients.

Compounds of the invention can also be used in the prevention of mycosis infections in patients with congenital or acquired immunodeficiency.

Compounds of the invention are not limited to pharmaceutical use, they can also be used as fungicides in fields other than pharmaceuticals.

Therefore a subject of the invention is antifungal compounds, compounds of formula (I) as well as their addition salts with acids.

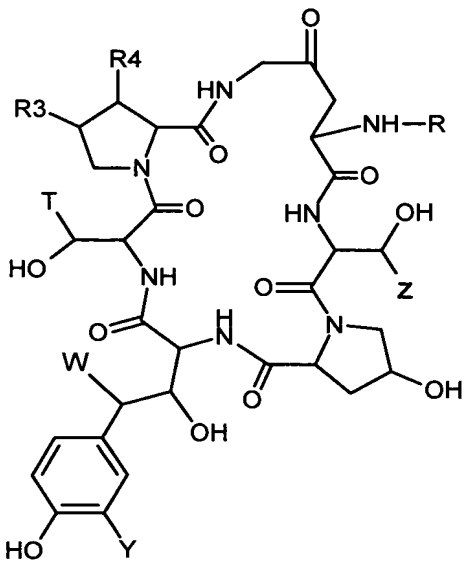
A subject of the invention is also compounds of formula (I), as medicaments.

A particular subject of the invention is pharmaceutical compositions containing as active ingredient at least one compound of formula (I) or one of its pharmaceutically acceptable addition salts with acids.

These compositions can be administered by buccal, rectal, parenteral route or by local route by topical application to the skin and mucous membranes, but the preferred route is the buccal route.

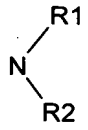
They can be solid or liquid and be presented in the pharmaceutical forms commonly used in human medicine, such as for example, plain or sugar-coated tablets, gelatin capsules, granules, suppositories, injectable preparations, ointments, creams, gels; they are prepared according to the usual methods. The active ingredient or ingredients can be incorporated with excipients usually used in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents, preservatives.

A subject of the invention is also a process for preparation of the compounds of formula (I) characterized in that a compound of formula (II)

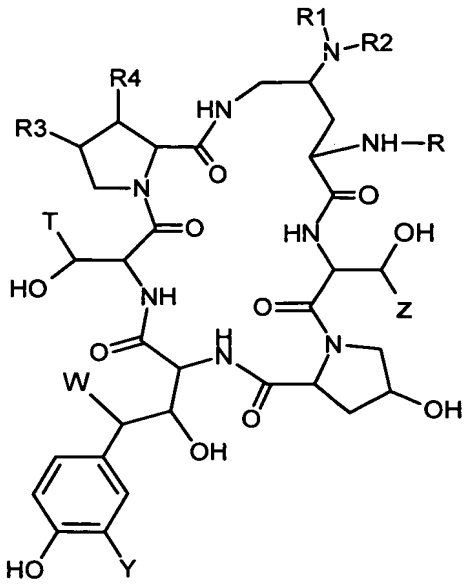


(II)

in which R, R3, R4, T, Y, W and Z retain their preceding meaning, is subjected to the action of an amine or an amine derivative capable of introducing

the  radical

in which R1 and R2 retain their preceding meaning and if desired to the action of a reducing agent and/or of an amine functionalization agent, and/or of an acid in order to form the salt of the product obtained, and/or of a separation agent of the different isomers obtained, and in this way the sought compound of formula (I) is obtained.

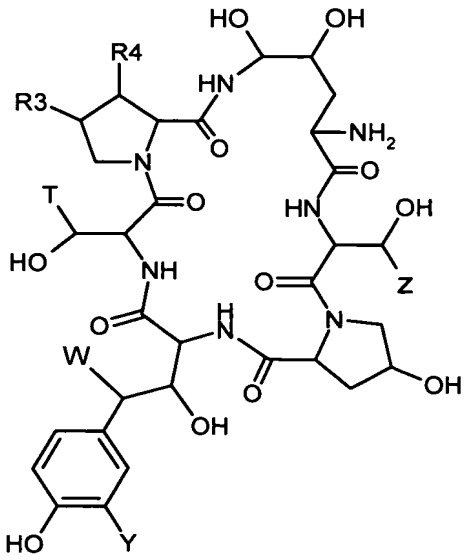


(I)

in which R1, R2, R3, R4, T, Y, W, R and Z retain their preceding meaning, then, if desired, the compound of formula (I) is subjected to the action of an acid in order to form the salt and, if desired, the different isomers obtained are separated.

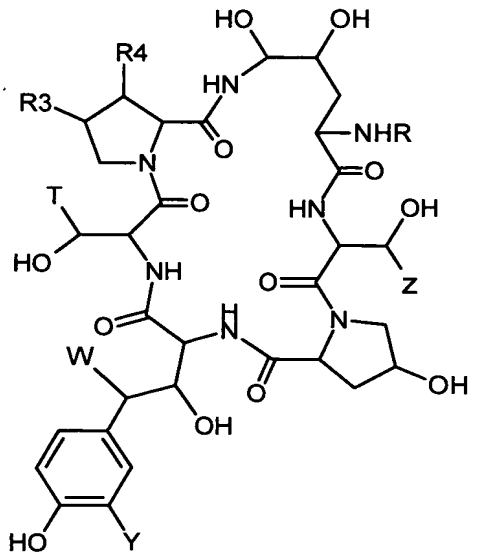
The new compounds of formula II used are new products and are themselves a subject of the invention.

A subject of the invention is also a process characterized in that a compound of formula (III)



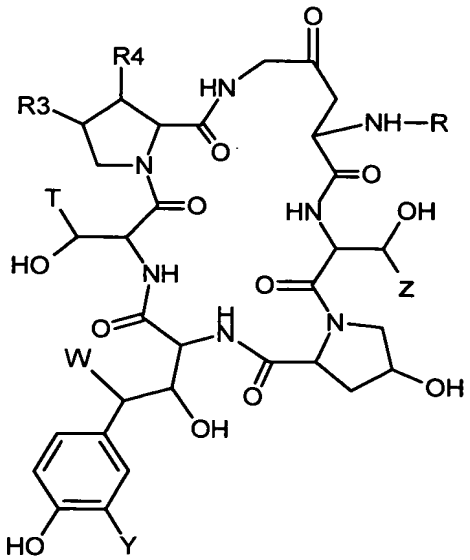
(III)

in which the different substituents retain their preceding meaning is subjected to the action of an agent capable of replacing NH2 by NHR, R retaining its preceding meaning in order to obtain the compound of formula (IV)



(IV)

which is subjected to the action of trimethylsilyl iodide in order to obtain the compound of corresponding formula (II).



(II)

The compounds of formula III and IV used are new products and are themselves a subject of the present invention.

Among the preferred products of formula III and IV, the products can in particular be mentioned, the preparation of which is given hereafter in the experimental part.

The following examples illustrate the invention without however limiting it:

Preparation 1: deoxymulundocandin "nucleus"

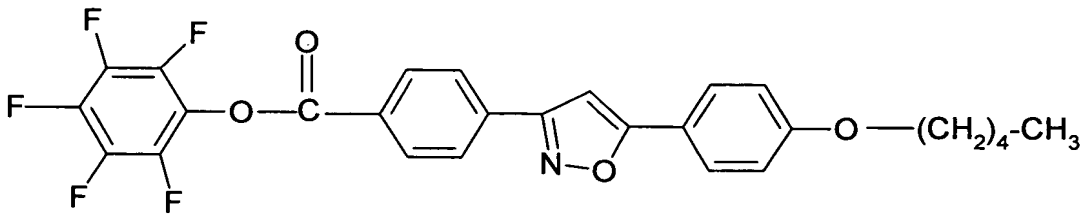
2 g of deoxymulundocandin is dissolved in 20 ml of DMSO. This solution is poured into a suspension containing 120 g of Actinoplanes utahensis FH2264 in 870 ml of a KH2PO4, K2HPO4 buffer (pH: 6.8). The reaction mixture is maintained under stirring for 70 hours at 30°C followed by filtration. The mycelium is washed with the phosphate buffer (pH: 6.8). The washing liquids and filtrate are combined. The product obtained is chromatographed on DIAION HP 20 resin and a product is obtained which is used as described hereafter.

EXAMPLE 1: 1-[4-[(2-aminoethyl)amino]-N2-[[4-[5-[4-pentyloxy)phenyl]-3-isoxazolyl]phenyl]carbonyl]-L-ornithine]-4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B (isomer A and isomer B).

STAGE A

1-[(4R,5R)-4,5-dihydroxy-N2-[[4-[5-[4-(pentyloxy)phenyl]isoxazol-3-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B.

16.8 g of the product of the preparation is introduced into 552 ml of DMF under stirring and a nitrogen atmosphere. Following stirring for 5 minutes 19 g of ester of formula



is added, followed by stirring for 29 hours, then filtration and concentration under reduced pressure. The residue is taken up in ether, followed by another trituration, washing with ethyl ether, chromatography on silica, eluting with methylene chloride/methanol mixture (85/15). The expected product is obtained in this way, rf = 0.24.

STAGE B

1-[4-oxo-N2-[[4-[5-[4-(pentyloxy)phenyl]isoxazol-3-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B.

6.12 ml of trimethylsilyl iodide is added to a suspension containing 16.1 g of the product of Stage A and 374 ml of acetonitrile. The reaction mixture is then heated for 15 minutes to 60°C followed by hydrolysis with a saturated sodium thiosulphate solution, drying under vacuum, then chromatography on silica eluting with methylene chloride, methanol, water mixture 86/13/1. The sought product is obtained, rf = 0.23.

Mass spectrum

MH+ = 1083.6

Mna+ = 1105.6

STAGE C

1-[4-[(2-aminoethyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-3-isoxazol-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate (Isomer A and isomer B).

8.6 mg of $NaBH_3CN$ is introduced into a mixture of 120 mg of product of the preceding stage, 2.4 ml of methanol, 60 mg of ethylenediamine diacetate in the presence of activated siliporite 4A. The reaction mixture is maintained under stirring and a nitrogen atmosphere for 18 hours. The product obtained is filtered, concentrated and purified by semi-preparative HPLC eluting with acetonitrile/H_2O/TFA mixture (40-60-0.02%). 14.5 mg of the sought product is recovered.

Mass spectrum

1127+ = MH+

1149+ = Mna+

The following are recovered: Isomer A: 14.5mg
Isomer B: 17.5 mg

EXAMPLE 2: Trans-1-[4-[(2-aminocyclohexyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate (Isomer A and Isomer B).
Approximately 40 µl of acetic acid is added, under stirring and under a nitrogen atmosphere until a pH close to 6 is obtained, to a solution containing 100 mg of the product obtained in the second to last stage of the preceding example, 3 ml of methanol, 32 mg of (1R,2R)(-)-1,2-diaminocyclohexane in the presence of activated siliporite 3A, followed by stirring for 5 minutes and introduction of 12 mg of NaBH3CN. The reaction mixture is maintained under stirring for 18 hours, followed by filtering and concentrating under reduced pressure. The product obtained is purified by semi-preparative HPLC eluent CH3CN, H2O, TFA 50-50-0.02 %.
Isomer A weight = 11 mg
Isomer B weight = 14 mg
Mass spectrum
1181.5 MH+

EXAMPLE 3: Trans-1-[4-[(2-aminocyclohexyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate (Isomer A and isomer B).
By operating as in Example 2 with (1S, 2S)-(-)-1,2 diaminocyclohexane, the following are obtained:
Isomer A = 7.4 mg
Isomer B = 10.8 mg
Mass spectrum
1181.5 = MH+

EXAMPLE 4: 1-[4-[(2(S)-aminopropyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate (Isomer A and isomer B).
By operating as in Example 1 the following are obtained:

Isomer A: 13 mg

Isomer B: 10 mg

EXAMPLE 5: Trans-1-[4-[(2-aminocyclohexyl)amino]-N2-[[4-[3-[4-(pentyloxy)phenyl]-1,2,4-oxadiazol-5-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate.

STAGE A

1-[(4R,5R)-4,5-dihydroxyN2-[[4-[3-[4-(pentyloxy)phenyl]-1,2,4-oxadiazol-5-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B.

By operating as in Example 1 Stage A, the sought product was obtained

STAGE B

1-[4-oxo-N2-[[4-[3-[4-(pentyloxy)phenyl]-1,2,4-oxadiazol-5-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B.

By operating as in Example 1 Stage B, the sought product was obtained:

Mass spectrum 1106.6 Ma = MNa+

1090.8 Ma = MH+

STAGE C

Trans-1-[4-[(2-aminocyclohexyl)amino]-N2-[[4-[3-[4-(pentyloxy)phenyl]-1,2,4-oxadiazol-5-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate.

By operating as in Example 1 Stage C, starting from 150 mg of the product of Stage B, and 51.4 mg of (1S,2S)1-2-diaminocyclohexane, 165 mg of crude product is obtained which is purified by semi-preparative HPLC (KROMASIL C18 column) (eluent: CH3CN/H2O/TFA 45/55/0.1).

The following are obtained:

Isomer A 10.8 mg

Isomer B 5.2 mg

Mass spectrum: 1204 = MN^+

1182 = MH^+

EXAMPLE 6: 1-[4-[(2-aminoethyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-1,3,4-thiadiazol-2-yl]phenyl]carbonyl]-L-

ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate.

STAGE A

1-[(4R,5R)-4,5-dihydroxy N2-[[4-[3-[4-(pentyloxy)phenyl]-1,3,4-thiadiazol-2-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B.

A suspension containing 2 g of 4-[5-[4-(pentyloxy)phenyl]-1,3,4-thiadiazol-2-yl]-benzoic acid, 30 ml of DMF and 30 ml of dioxane is stirred for 5 minutes at 20°C and 1.55 ml of tributylamine, 7.74 ml of isobutyl chloroformate are added at 0/±5°C, followed by stirring for 3 minutes at 0±5°C then 3 hours at ambient temperature. 4.53 g of deoxymulundocandin nucleus is introduced, the reaction mixture is stirred overnight at 20°C, and concentrated to dryness. The residue is taken up in ethyl ether, followed by separation, washing in ethyl ether, and drying. 7.8 g of product is obtained, which is purified by chromatography on silica, eluting with a methylene chloride-methanol-water mixture 86-13-1. 2.51 g of sought product is obtained.

STAGE B

1-[4-oxo-N2-[[4-[5-[4-(pentyloxy)phenyl]-1,2,4-thiadiazol-2-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B.

By operating as in Example B of Example 1, the sought product is obtained.

STAGE C

1-[4-[(2-aminoethyl)amino]-N2-[[4-[3-[4-(pentyloxy)phenyl]-1,3,4-thiadiazolol-2-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B.

By operating as in Example 1, Stage C starting from the product of the preceding stage and ethyldiamine diacetate, the sought product is obtained.

Isomer A weight = 8 mg

Isomer B weight = 9 mg.

EXAMPLE 7: Trans 1-[4-[(2-aminocyclohexyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-1,3,4-thiadiazol-2-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-

echinocandin B trifluoroacetate

By operating as in Example 1, starting from the product of Stage B of Example 5 (50 mg) and (1S,2S)(+)1,2 diaminocyclohexane (15.6 mg), the sought product is obtained.

Isomer A = 4 mg

Isomer B = 6.5 mg

EXAMPLE 8: Trans 1-[4-[(2-aminocyclohexyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-1,2,4-thiadiazol-2-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate (Isomer A and isomer B)

By operating as in Example 1 Stage C starting from the product of the Stage B of Example 5 (50 mg) and 1R, 2R, 1,2-diaminocyclohexane (15.6 mg), the sought product is obtained.

Isomer A = 8.8 mg

Isomer B = 10.6 mg

EXAMPLE: Pharmaceutical composition:

Tablets were prepared containing:

- Product of Example 1..... 150 mg
- Excipient s.q.f..... 1 g

(Detail of the excipient: starch, talc, magnesium stearate).

PHARMACOLOGICAL STUDY

A - Inhibition of the glucan synthase of Candida albicans.

Candida albicans membranes were purified according to the process described by Tang et al, Antimicrob. Agents Chemother 35, 99-103, 1991. 22.5 µg of membrane proteins are incubated in a mixture of 2Mm of 14C-UDP glucose (specific activity = 0.34 mCi./mmol, 50 µg of α-amylase, 1Mm of dithiothreitol (DTT), 1Mm EDTA, 100Mm NaF, 7µM of GTP-γ-S, 1M of sucrose and 50Mm of Tris-HCL (pH 7.8) in a volume of 100 µl. The medium is incubated at 25°C for 1 hour and the reaction terminated by adding TCA at a final concentration of 5%. The reaction mixture is transferred to a pre-moistened glass fibre filter. The filter is washed, dried and its radioactivity is counted. Mulundocandin is used as a positive control.

Control of the vehicle is carried out with the same quantity of 1% DMSO. The results obtained show that the products of

the invention have good activity in this test, in particular the products of Example 1.

B - activity on the Aspergillus fumigatus enzyme.

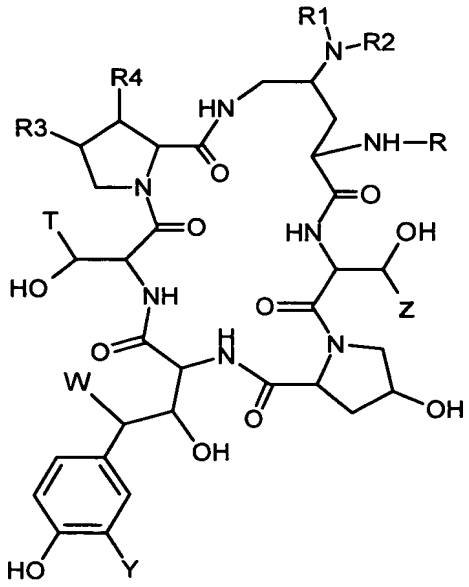
The enzyme is prepared according to the process of Beaulieu et al.(Antimicrob. Agents Chenother 38, 937-944, 1994.

The protocol used is identical with the protocol described above for the Candida albicans enzyme except that dithiothreitol is not used in the reaction mixture.

The products show good activity in this test.

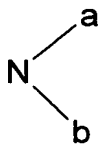
CLAIMS

1) In all possible isomeric forms as well as their mixtures, the compounds of formula (I):

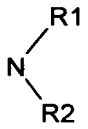


(I)

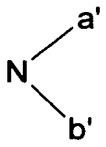
in which
either R1 and R2 which are identical to or different from one another, represent a hydrogen atom, a hydroxyl radical, a linear, branched or cyclic alkyl radical containing up to 8 carbon atoms optionally interrupted by an oxygen atom optionally substituted by a halogen atom,

an OH radical, an  radical, a and b being

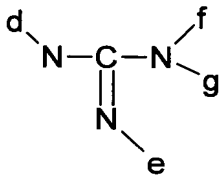
identical to or different from one another,
representing a hydrogen atom or an alkyl radical containing up to 8 carbon atoms, a and b can optionally form with the nitrogen atom a heterocycle optionally containing one or more additional heteroatoms,
- or R1 forms with the endocyclic carbon atom

carrying the  radical a double bond and or R2

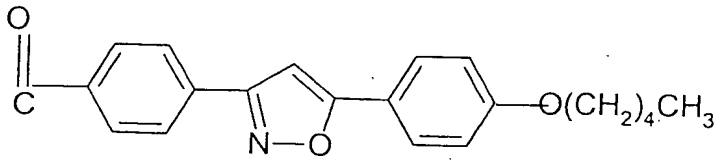
represents an Xra radical, X representing an oxygen atom or an NH or N-alkyl radical containing up to 8 carbon atoms and Ra represents a hydrogen atom, a linear, branched or cyclic alkyl radical containing up to 8 carbon atoms optionally substituted by one or more halogen atoms, by one or more OH, CO2H, CO2alk radicals,
by an

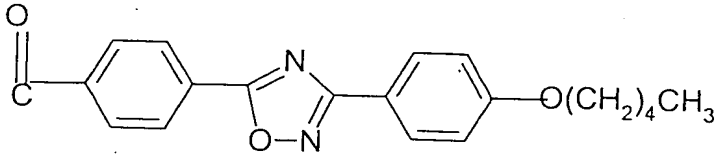


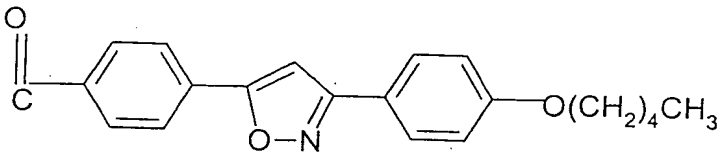
radical, a' and b' representing a hydrogen atom, an alkyl radical containing up to 8 carbon atoms, a' and b' can form a heterocycle optionally containing one or more additional heteroatoms and/or by a heterocycle containing one or more heteroatoms or R2 represents a

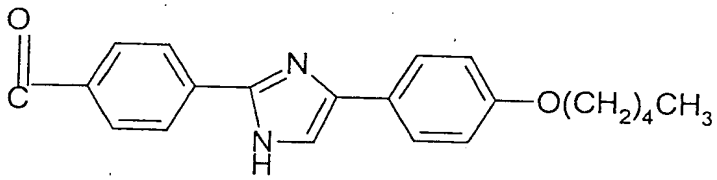


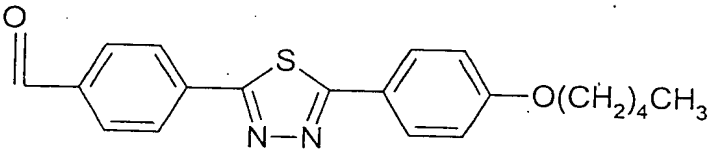
radical in which d, e, f and g represent a hydrogen atom or an alkyl radical containing up to 8 carbon atoms, f and g can moreover represent an acyl radical containing up to 8 carbon atoms, e and f can also form a ring optionally containing one or more heteroatoms,
R3 represents a hydrogen atom, a methyl or hydroxyl radical
R4 represents a hydrogen atom or a hydroxyl radical
R represents a radical chosen from the following radicals:

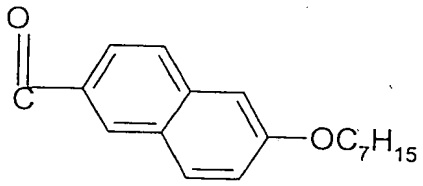


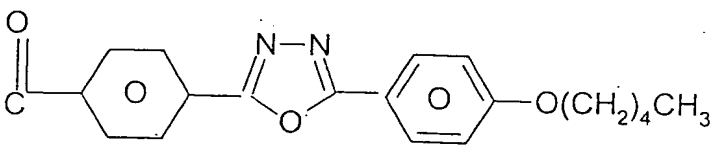


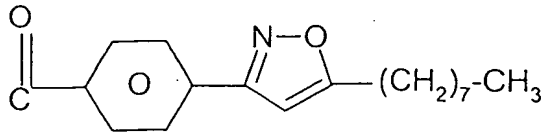












T represents a hydrogen atom, a methyl radical, a CH2CONH2, CH2CN radical, a (CH2)2NH2 or (CH2)2Nalc$^{+}X^{-}$ radical, X being a halogen atom and alk an alkyl radical containing up to 8 carbon atoms,

Y represents a hydrogen atom, a hydroxyl radical or a halogen atom or an OSO3H radical or one of the salts of this radical,

W represents a hydrogen atom or an OH radical,

Z represents a hydrogen atom or a methyl radical,

as well as the addition salts with acids of products of formula (I).

2) The compounds of formula (I) defined in claim 1 in which T represents a hydrogen atom.

3) The compounds of formula (I) defined in claim 1 or 2 in which W represents a hydrogen atom.

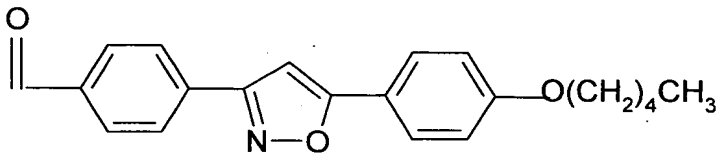
4) The compounds of formula (I) defined in any one of claims 1 to 3, in which Z represents a methyl radical.

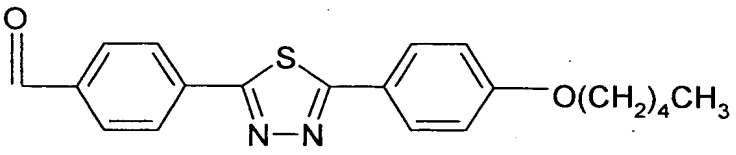
5) The compounds of formula (I) defined in any one of claims 1 to 4 in which Y represents a hydrogen atom.

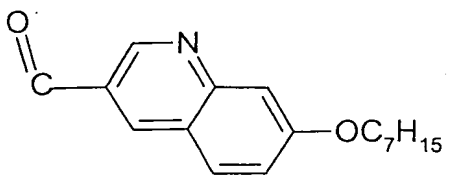
6) The compounds of formula (I) defined in any one of claims 1 to 5 in which R3 represents a methyl radical.

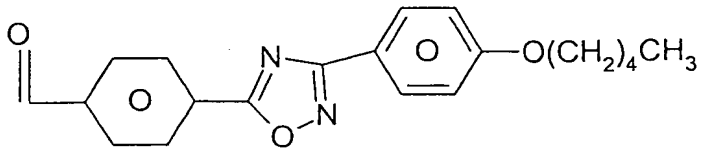
7) The compounds of formula defined in any one of claims 1 to 6 in which R4 represents a hydroxyl radical.

8) The compounds of formula (I) defined in any one of claims 1 to 7 in which R represents a

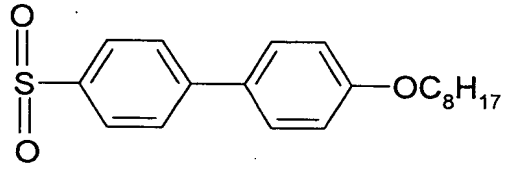








radical or a



radical.

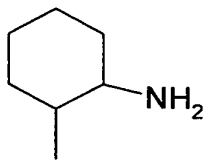
9) The compounds of formula I defined in any one of claims 1 to 8 in which R1 represents a hydrogen radical.

10) The compounds of formula defined in any one of claims 1 to 9 in which R2 represents a

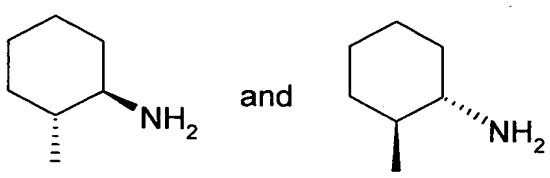
(CH2)2 NH2

radical.

11) The compounds of formula I defined in any one of claims 1 to 9 in which R2 represents a

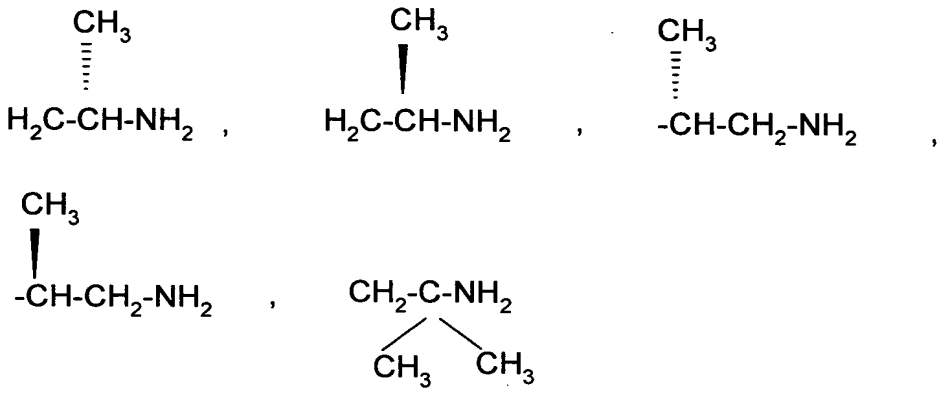


radical and in particular the



radicals.

12) The compounds of formula I defined in any one of claims 1 to 9 in which R2 represents a



radical.

13) The compounds of formula I defined in claim 1 the names of which follow:

- 1-[4-[(2-aminoethyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-3-isoxazol-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate,

- trans-1-[4-[(2-aminocyclohexyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate,

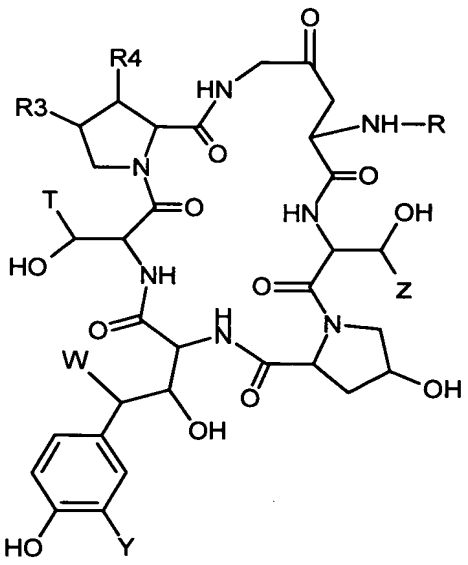
- 1-[4-[(2(S)-aminopropyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate,

- 1-[4-[(2-aminoethyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-1,3,4-thiadiazol-2-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate,

- trans 1-[4-[(2-aminocyclohexyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-1,3,4-thiadiazol-2-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate,

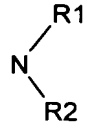
- trans 1-[4-[(2-aminocyclohexyl)amino]-N2-[[4-[3-[4-(pentyloxy)phenyl]-1,2,4-oxadiazol-5-yl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate.

14) Process for the preparation of compounds of formula (I) defined in any one of claims 1 to 15, characterized in that a compound of formula (II)



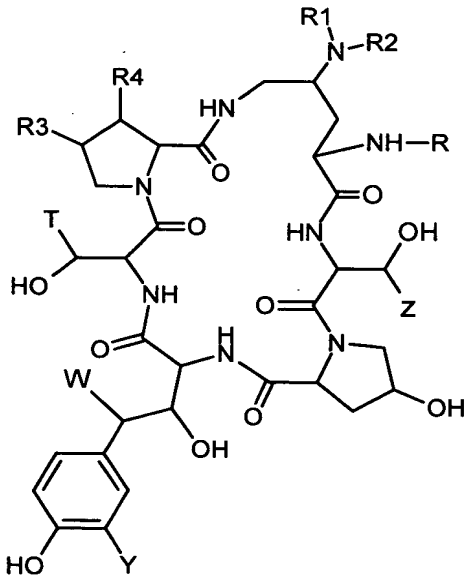
(II)

in which R, R3, R4, T, Y, W and Z retain their preceding meaning, is subjected to the action of an amine or an amine derivative capable of introducing



the radical in which R1 and R2

retain their preceding meaning and if desired to the action of a reducing agent
and/or of an amine functionalization agent,
and/or of an acid in order to form the salt of the product obtained,
and/or of a separation agent of the different isomers obtained,
and in this way the desired compound of formula (I) is obtained.



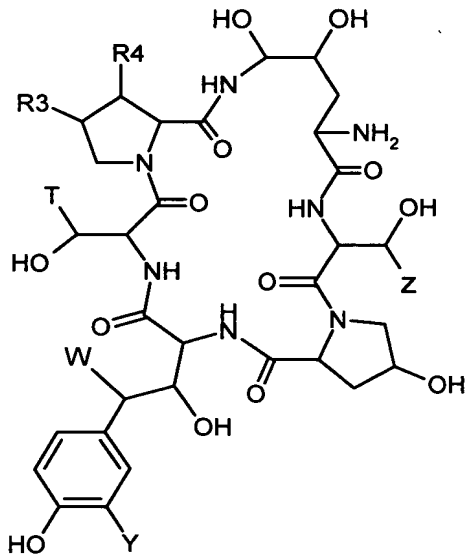
(I)

in which R1, R2, R3, R4, T, Y, W, R and Z retain their preceding meaning, then, if desired, the compound of formula (I) is subjected to the action of an acid in order to form the salt and, if desired, the different isomers obtained are separated.

15) As new chemical products, the compounds of formula (II) defined in claim 14.

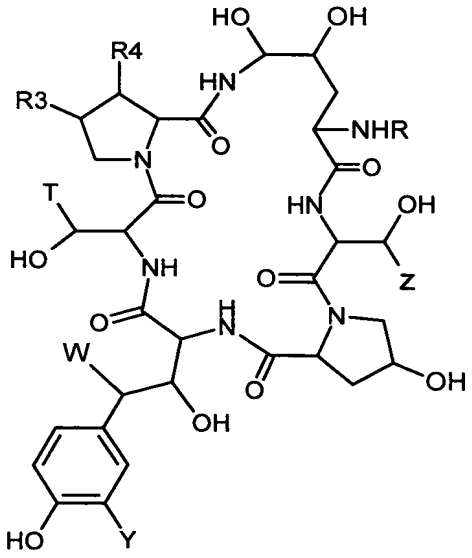
16) Process according to claim 14 characterized in that a

compound of formula (III)



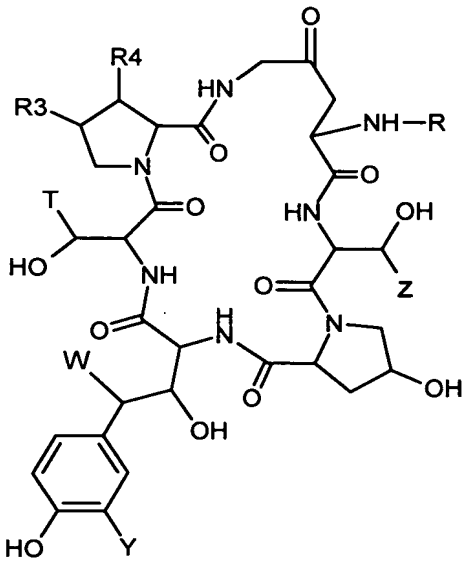
(III)

in which the different substituents retain their preceding meaning is subjected to the action of an agent capable of replacing NH2 by NHR, R retaining its preceding meaning in order to obtain the compound of formula (IV)



(IV)

which is subjected to the action of trimethylsilyl iodide in order to obtain the corresponding compound of formula (II)

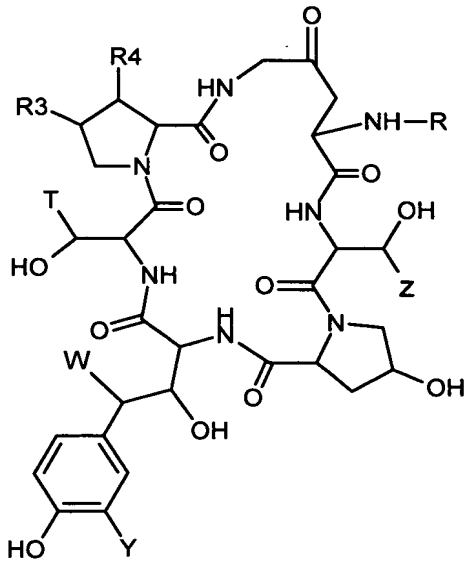


(II)

17) As new chemical products the compounds of formulae III and IV as defined in claim 16.

18) As antifungal compounds, the compounds of formula (I) defined in any one of claims 1 to 13, as well as their addition salts with acids.

19) The pharmaceutical compositions containing as a medicament at least one compound of formula (I) defined in any one of claims 1 to 13, as well as their addition salts with pharmaceutically acceptable acids.



17) As antifungal compounds, the compounds of formula (I) defined in any one of claims 1 to 13, as well as their addition salts with acids.

18) The pharmaceutical compositions containing as a medicament at least one compound of formula (I) defined in any one of claims 1 to 13, as well as their addition salts with pharmaceutically acceptable acids.